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CORRECTION OF NON-MOTOR VEGETATIVE FLUCTUATIONS WITH PARKINSON'S DISEASE BASED ON LEVODOPA TREATMENT

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Abstract

The influence of dopamine receptor agonists in the transdermal and oral forms of drugs and amantadine for a non-motor autonomic fluctuations of patients with different duration of the disease during the treatment of Parkinson's in a stable dose of levodopa were established. It was analysed, that the use of dopamine receptor agonists in the transdermal and oral forms of drugs reduce the frequency and duration of vegetative non-motor fluctuations of patients with Parkinson's disease. The use of amantadine sulphate has little effect in a decrease of non-motor autonomic fluctuations

Key words: Parkinson's disease, non-motor fluctuations, levodopathrapy.

Parkinson's disease - is a steadily progressive neurodegenerative disease characterized by a gradual increase in motor, mental and autonomic disorders.

But despite the advances in the treatment of the disease, it retains a progressive course and inevitably leads to disability of patients [1,2].

As the disease progresses in its clinical picture non-motor manifestations are getting increasingly important, which can largely affect the quality of life of patients and their degree of disability than the classic motor symptoms of Parkinson's disease [2-5].

Non-motor fluctuations arise mainly during the "off" time and decrease or disappear after levodopa administration. All non-motor symptoms that occur with different phases of levodopa action are divided into the following groups: vegetative, mental and sensory. Vegetative fluctuations dominate in the clinical picture of non-motor symptoms [1-4,6-9]. The appearance of the fluctuations depends on the severity and duration of the disease stage at Hoen and Yahr, the duration of use and the dose of levodopa [5,6,8-10]. When disease onset early fluctuations appear faster and are pronounced. Some role of gender factors: women's autonomic fluctuations are observed more frequently than men's ones [2,9,10].

Non-motor manifestations may outpace the development of the disease and motor worsening may persist after the reduction of symptoms of Parkinson's disease. This is explained by the involvement of the basal ganglia and closely related limbic, diencephalic, brainstem struc-

tures, the frontal cortex [2,7-12]. The approaches to treatment of non-motor fluctuations are not well developed, but should be based on the same principles as the correction of motor fluctuations. It is important to establish clearly in which phase of certain symptoms appear [2,5-9].

The aim of our study was to investigate the influence of dopamine receptor agonists in the transdermal and oral forms of drugs and amantadine on non-motor autonomic fluctuations of patients with a different duration of the disease during the treatment of Parkinson's is a stable dose of levodopa.

Material and methods. We examined 30 patients (20 women and 10 men) with an akinesic-tremor form of Parkinson's disease who were treated in the neurology department of Poltava Regional Clinical Hospital by N.V.Sklifosovsky and observed in the center of Parkinson at the Department of Nervous Diseases with neurosurgery and medical genetics HSEEU "Ukrainian Medical Dental Academy". Diagnosis was made according to the standard of the International Classification of Diseases of the X revision. The verification of the diagnosis of Parkinson's disease was carried out according to the international clinical diagnostic criteria of the Bank of the brain of Parkinson's Disease Society of Great Britain. The severity of disease was determined by the rating scale Unified Parkinson's Disease Rating (UPDRS).

The average age was 60.5 ± 10.8 years. The average duration of disease - 10.9 ± 4.5 years. The stage of the disease was evaluated on a scale Hoen and Yahr. The rating vegetative state of

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patients was conducted by a questionnaire to assess autonomic functions. The quality of life of patients was determined by PDQ-39 scale. All patients received continuous therapy with levodopa drugs 4 times a day (daily dose of levodopa was 375-500 mg). The disease severity on a scale Hoen and Yahr was - 3.5 ± 0.5 .

By the method of the treatment, patients were divided into three groups: group I (10 patients) - the duration of receiving levodopa 7.3 ± 1.5 years - received rotigotine as a transdermal patch in the form of "Neupro" 8 mg 1 time a day for 3 weeks; group 2 (10 patients), the duration of receiving levodopa 6.6 ± 1.4 years - pramipexole as a drug "Pramipex" 1.5 mg per day for three divided doses for 3 weeks (after gradual, within 3 weeks of titration dose); group 3 (10 patients),

the duration of treatment with levodopa 4.3 ± 1.6 years - received amantadine sulfate oral dose of 300 mg a day in three divided doses for 3 weeks. The control group - 10 patients (4 women and 6 men), duration of treatment with levodopa 5.2 ± 1.8 years, which were treated only by levodopa 4 times a day (the duration of receiving levodopa 3.1 ± 0.9 years).

The general clinical, neurological and neuropsychological examination was carried out for all patients at the beginning and end of treatment. The patients kept diaries to assess periods of activation, deactivation, and appearances non-motor fluctuations of throughout the study.

Results and discussion. Features of autonomic disorders were evaluated on a scale of UPDRS. Autonomic fluctuations are shown in Table 1.

Table 1
Patient's basic autonomic dysfunction with Parkinson's disease at the beginning of treatment (%)

Signs	I group (n=10)	II group (n=10)	III group (n=10)	Control (n=10)
Hyperhydrosis	60	55	55	50
Feeling hot/cold	20	10	10	20
Hypersalivation	40	50	50	30
Abdominal discomfort	20	30	20	20
Frequent urination/dysuria/incontinence	50	30	30	30
Sexual dysfunctions	40	35	40	20
Orthostatic hypotension	10	5	10	10
Dyspnea/compulsive cough	20	10	30	20
Constipation	70	60	60	70

Table 2
The emergence of non-motor symptoms of autonomic in the action phase of levodopa (%)

Signs	I group (n=10)		II group (n=10)		III group (n=10)		Control (n=10)	
	Period «on»	Period «off»	Period «on»	Period «off»	Period «on»	Period «off»	Period «on»	Period «off»
Hyperhydrosis	10	50	20	40	20	50	30	60
Feeling hot/cold	10	40	20	30	10	40	10	40
Hypersalivation	20	50	30	40	20	50	40	60
Abdominal discomfort	20	30	10	40	20	50	10	30
Frequent urination/dysuria/incontinence	20	60	10	40	20	30	10	50
Orthostatic hypotension	10	20	10	30	20	20	10	10

The highest frequency of autonomic disorders observed in all three groups of women and was presented in the form of constipation, dysurinal disorders, hyperhidrosis, hypersalivation. The non-motor autonomic dysfunctions are more pronounced during the "off" action of levodopa. Sometimes biphasic fluctuations are observed (Table 2).

You can see from the table 2 the most frequent autonomic fluctuations appeared in "off" period: sweating (50% of the off period in the first group and 60% - in the second group of patients), salivation (50% in the first and second groups during the 60% off - in the control group

of patients), the feeling hot and cold, urinary disorders. Hypersalivation can indirectly be attributed to the non-motor autonomic symptoms, because it depends of directly on swallowing function. However, a proved stimulating effect of levodopa on saliva production.

The rare vegetative manifestations include: abdominal discomfort, orthostatic hypotension, nausea, respiratory function as breathlessness, chest's discomfort or compulsive cough. In the course of the study, after treatment in groups of patients there were changes in autonomic manifestations fluctuations (Table 3).

Table 3
Patient's basic autonomic dysfunction with Parkinson's disease at the beginning of treatment (%)

Signs	I group (n=10)	II group (n=10)	III group (n=10)	Control (n=10)
	Period «off»	Period «off»	Period «off»	Period «off»
Hyprehidrosis	30*	10*	30*	60
Feelings hot/cold	40	10*	30	40
Hypersalivation	40	20	40	60
Abdominal discomfort	10	20	40	30
Frequent urination/dysuria/ incontinence	20*	20	30*	50
Orthostatic hypotension	40*	10	10	10

Note: * - $p < 0.05$ - compared with the group of patients before and after treatment.

After treatment there was a positive effect as a decrease in non-motor vegetative symptoms in groups, treated with rotigotine and pramipaxole. In the first group of patients, who were treated with rotigotine, an increased incidence of orthostatic hypotension was noticed, but cases of hypotension were observed in other groups of patients. Most likely a symptom of the advanced stage of the disease of older patients. However, the presence of orthostatic hypotension may be due to the amplification of dopaminergic therapy (dopamine receptor agonists). Some patients had cutaneous manifestations in the form of itching, redness at the place of transdermal patch application.

The positive results were found in groups of patients treated with pramipexole and amantadine sulfate. More rapid effect was observed when pramipexole was used at a dose of 1.5 mg per day (the second group of patients).

Conclusion. Thus, as a result of studies, the positive results obtained in the form of reducing the frequency and duration of vegetative non-motor fluctuations of patients with Parkinson's disease. It's found that the use for rotigotine has a positive effect, but it is desirable to use in the elderly and young people with Parkinson disease in the absence of orthostatic hypotension and allergic reactions in anamnesis.

Using amantadine sulphate has little effect, compared to the effect on levodopa-induced motor dyskinesia. The application of a dopamine receptor agonist in the form of a transdermal patch and oral drugs in average therapeutic dose (1.5 mg) has a positive effect and may be recommended for the non-motor vegetative fluctuations correction for Parkinson's disease patients on the base of levodopa treatment in a stable dose.

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РЕЗЮМЕ

КОРРЕКЦИЯ НЕМОТОРНЫХ ВЕГЕТАТИВНЫХ ФЛУКТУАЦИЙ ПРИ БОЛЕЗНИ ПАРКИНСОНА НА ФОНЕ ЛЕВОДОПАТЕРАПИИ

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Проведено изучение влияния агонистов дофаминовых рецепторов в виде трансдермальной формы и пероральных препаратов и амантадинов на течение немоторных вегетативных флуктуаций у больных с разной длительностью течения болезни Паркинсона на фоне стабильной дозы леводопы. Отмечено, что применение агонистов дофаминовых рецепторов в виде трансдермальной и пероральной форм имеет положительный эффект в виде снижения частоты и длительности вегетативных немоторных флуктуаций у пациентов с болезнью Паркинсона. Использование амантадина сульфата оказывает незначительный эффект на леводоп-индуцируемые моторные дискинезии.

Ключевые слова: болезнь Паркинсона, немоторные флуктуации, леводопотерапия.